The claims are not amended in this paper. Applicants believe that all of the rejections have been fully responded to in the Response filed March 2, 2001. The following is merely a summary of allele - disease relationships as requested by the Examiner and as pertains to the rejection under 35 U.S.C. § 112, first paragraph, enablement.

REJECTION OF CLAIMS 1-14, 37-42 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

"Enablement"

The Examiner argues, "The disclosure fails to enable the claimed invention because it does not provide convincing biochemical evidence which links the overexpression of IL-1B to any disease, and because no such evidence is present in the prior art."

As previously made of record, Applicants respectfully maintain that the specification does provide evidence that overexpression of IL-1B is linked to many diseases.

Applicants note that one of skill in the art can practice the claimed invention regardless of whether or not the IL-1B (+6912) allele 2 causes overexpression of IL-1B in any disease. As described in the previously filed Declaration of Dr. Francesco di Giovine, an allele may be associated with a disorder, and therefore be of prognostic value, whether or not that allele causes the disorder in question. An allele may be considered associated with a disorder if it is linked (or in "linkage disequilibrium" with) an allele that is itself known to be associated with a disorder (for a discussion of these issues, see WO 98/54359, cited by the Examiner, pp.1 - 2).

The linkage analysis presented in Example 6 (for example) demonstrates that the IL-1B (+6912) allele 2 is in linkage disequilibrium with alleles of the IL-1 (33221461) haplotype, and will therefore be useful for determining a predisposition to disorders that are associated with one or more alleles of this haplotype. For example, IL-1B (+3954) allele 2 has been directly associated with periodontal disease, insulin-dependent diabetes and asthma, and indirectly associated with a suite of other disorders as a part of the IL-1 (33221461) haplotype (see below). Therefore, the detection of IL-1B (+3954) allele 2 in a subject indicates that the subject is predisposed to each of those disorders. The instant application teaches (see for example, pp. 44-

46 and Table 3) that subjects carrying the IL-1B (+3954) allele 2 are greater than 99% likely to carry IL-1B (+6912) allele 2. Therefore detecting the IL-1B (+6912) genotype will be at least as predictive as detecting the IL-1B (+3954) allele 2.

Applicants contend that information regarding disorders associated with each of the alleles of the IL-1 (33221461) haplotype are provided in references cited throughout the specification (see for example, page 2, lines 10-25). A tabular summary of this information may be found in the attached Exhibit A (WO 01/00880, see pages 20-1). For the Examiner's convenience, the table is reproduced below. Note that IL-1A (-889) allele 2, IL-1A (+4845) allele 2, IL-1B (+3954) are among the alleles known to belong to the IL-1 (33221461) haplotype.

TABLE 1

Association Of IL-1 Haplotype Gene Markers With Certain Diseases

GENOTYPE	IL-1A (-889)	IL-1A (+4845)	IL-1B (-511)	IL-1B (+3954)	IL-1RN (+2018)
DISEASE					
Periodontal Disease	(*2)	*2		*2	
Coronary Artery Disease			*2		*2
Atherosclerosis					
Osteoporosis					*2
Insulin dependent diabetes				*2	
Diabetic retinopathy					*1
Endstage renal diseases					(+)
Diabetic nephropathy					*2
Hepatic fibrosis (Japanese alcoholics)					(+)
Alopecia areata					*2
Graves' disease					*2
Graves' ophthalmopathy					(-)
Extrathyroid disease					(+)
Systemic Lupus Erythematosus					*2

Lichen Sclerosis					*2
Arthritis					(+)
Juvenile chronic arthritis	*2				
Rheumatoid arthritis					(+)
Insulin dependent diabetes				*2	*2 VNTR
Ulcerative colitis					*2
Asthma			*2	*2	
Multiple sclerosis				(*2)	*2VNTR
Menopause, early onset					*2

Although each of the alleles of the IL-1 (33221461) haplotype is understood to have predictive value for disease associations attributed to all the alleles of the haplotype, direct correlations between certain alleles and certain diseases have also been established.

With respect to the IL-1B (+3954) allele, each of these associations may be found, for example, in the references below:

Periodontal disease: US Patent 5,686,246 (see IDS Document No. AA)
Insulin dependent diabetes: Pociot et al. *Eur. J. Clin. Invest.* 22: 396-402 1992 (see IDS Doc. No. BB)
Asthma: US Patent 6,140,047 (attached as Exhibit B).

With respect to the IL-1A (-889) allele, the association with juvenile chronic arthritis is presented, for example, in McDowell et al. *Arthritis Rheum.* 38:221-28 1995 (see IDS Doc. No. AY).

Applicants respectfully conclude that the Application meets the requirements for enablement under 35 U.S.C. § 112, first paragraph. Reconsideration and withdrawal of this rejection is respectfully requested.

CONCLUSION

For the foregoing reasons and reasons previously made of record, Applicants respectfully request reconsideration and withdrawal of all pending rejections. Applicants believe that the claims, both those originally filed and those newly added, are now in condition for allowance and early notification to this effect is earnestly solicited. If the Examiner believes that an interview would expedite the prosecution of this application, the Applicants would ask that the Examiner please contact their representative identified below at the Examiner's convenience.

If there are any other fees due in connection with the filing of this Response, please charge the fees to our Deposit Account No. 06-1448. If a fee is required for an extension of time under 37 C.F.R. §1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

FOLEY, HOAG& ELIOT

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